

# Review of: "Targeting Alzheimer's disease hallmarks with the Nrf2 activator Isoeugenol"

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Potential competing interests: No potential competing interests to declare.

**Title of the manuscript:** Targeting Alzheimer's disease hallmarks with the Nrf2 activator Isoeugenol

## **Manuscript Number:**

The present study was designed to evaluate the therapeutic effects of Isoeugenol, a skin

allergen with electrophilic properties, in Alzheimer's disease by activating Nrf2 and reverting some AD hallmarks both *in vitro* and *in vivo*. The goal of looking for new products for AD treatment is timely and clinically relevant. The manuscript is well-written with sound methodology and novel findings. However, I also believe that a major revision of the manuscript is necessary as follows (All revised sentences must be highlighted (yellow highlight) in the revised manuscript):

1. Introduction and discussion should be shortened and partly rewritten to make them more consistent.
2. There are many displayed headings presented in the results and methods section. Some headings can be merged.
3. Results, 3-3 sections: Why did the authors not evaluate the Nrf2 levels in N2a-wt cells?
4. It is not clear why the authors used different times and concentrations of Isoeugenol in different tests. For example, in the 3-3 section: 5, 15, and 30 min for Akt and GSK3B, but 2, 4, and 6 hrs for Nrf2; in the 3-4 section: 1, 3, and 6 hrs for gene expression but 24 hrs for protein expression; in the 3-6 section: a 50 mg concentration of Isoeugenol was used (why were other concentrations not selected?); in the 3-5 section: 18 hrs for gene expression but 24 hrs for protein expression; etc....
5. Figures 4B, 5A, and 5D: Why is the control group missing?
6. Why did the authors study female mice in the 2-2-4-1 section and male mice in the 2-2-4-4 section? Why was the same gender not chosen for different tests?
7. Figure 11: Authors should indicate physiological changes and details of histological figures within the figure with arrows.
8. Please identify the statistical analysis in all figures.
9. All revised sentences must be highlighted (yellow highlight) in the revised manuscript.